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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/915,549	07/27/2001	Rainer H. Muller	662-57773	7384

20736 7590 01/13/2003

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EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 01/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/915,549	Applicant(s) MULLER, RAINER H.	
	Examiner Humera N. Sheikh	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2002 (paper no.7)* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-148* is/are pending in the application.

4a) Of the above claim(s) *16-18,67-142,145 and 147* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,19-66,143,144,146 and 148* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

Acknowledgement is made of the receipt of the Drawings, Extension Fee and the IDS, all filed 12/03/01 and the Election *without* traverse filed 10/22/02.

Claims 16-18, 67-142 and 145 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7. The applicant elected Group I (claims 1-66 and 143-148), species (a) oil-in-water emulsion and election of administration species (c) parenterally, intravenously, intra- and subcutaneously, intramuscularly, intra-articularly or intraperitoneally, without traverse.

Claims 1-15, 19-66, 143, 144, 146 and 148 are now pending. Claims 16-18, 67-142, 145 and 147 have been *withdrawn*. Claims 1-15, 19-66, 143, 144, 146 and 148 are rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 contains the trademark/trade names *Span 85* and *Tween 80*, on page 28, lines 26 and 27, respectively. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe *emulsifiers* and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-15, 19-25, 33-35, 37-46, 48, 55-57, 61-63, 143, 144, 146 and 148 are rejected under 35 U.S.C. 102(b) as being anticipated by *Davis* (EPO 0 296 845).

Davis discloses a dispersion comprising an oil-in-water emulsion containing a poorly soluble active ingredient (antifungal - Amphotericin B), wherein the emulsions are administered parenterally (i.e., intravenously, subcutaneously, intramuscularly) (see reference columns 2 line 15 through col. 4, line 35).

Claims 1-11, 19-25, 33-35, 37-45, 48, 55-57, 61-63, 143, 144, 146 and 148 are rejected under 35 U.S.C. 102(b) as being anticipated by Kaufman *et al.* (US Pat. No. 5,616,330, collectively, "Kaufman").

Kaufman discloses stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water (see abstract); (col. 1, line 64 through col. 2, line 60).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15, 19-66, 143, 144, 146 and 148 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Davis* (EPO 0 296 845) alone *or* Kaufman et al. (US Pat. No. 5,616,330, collectively, "Kaufman") alone.

Davis teaches a dispersion comprising an oil-in-water emulsion containing a poorly soluble active ingredient (antifungal - Amphotericin B), wherein the emulsions are administered parenterally (i.e., intravenously, subcutaneously, intramuscularly) (see reference columns 2 line 15 through col. 4, line 35). The emulsions are stable and reduce the toxicity of the drug. Davis teaches that the invention provides an oil-in-water surfactant-stabilized emulsion of a drug, wherein the drug is poorly soluble in both oil and water (col. 2, lines 15-19).

The drug used in this instance is the antibiotic, Amphotericin B. However, the drug may be any selected from a general or local anesthetic, hypnotic, sedative, antibiotic or anti-microbial, anti-neoplastics or immunosuppresants (col. 3, lines 3-19).

The surfactant used is preferably lecithin or phosphatidyl choline. The amount of surfactant used may be from 0.5 to 10% (col. 4, lines 10-12). This range clearly meets the applicant's claimed amount of less than 15 wt.%. The amount of oil in the final emulsion taught is suitably 5% to 50%. Any pharmaceutically acceptable oil may be used, for example, soybean or safflower oil or medium chain triglycerides or monoglycerides (col. 4, lines 3-9). The level of drug can be up to 1mg/ml, in the case of Amphotericin B.

The emulsions are usually administered parentally, for example by continuous venous infusion or by injection, which may be intravenous, subcutaneous or intramuscular (col. 4, lines 19-31). The examples demonstrate the teachings of emulsions using Amphotericin B in various conditions. For instance, Example 1 demonstrates an intravenous emulsion with amphotericin B (50 mg), wherein the drug was dissolved in methanol (100 ml). The oil used in this case was soya oil (10 ml) and the emulsifier used was (1.2 g) egg phosphatidylcholine dispersed in 90 ml water. Other suitable emulsifiers can also be used, such as poloxamer, poloxamine series (col. 5, line 30 through col. 6, line 21). Example 3 shows emulsions of amphotericin B resulting in a small particle size of less than 200 nm average diameters. Similarly, Example 5, demonstrates emulsion droplet sizes, measured by a laser diffraction sizer, wherein majority of droplets were less than 1 micron diameter (col. 7, line 20 through col. 8, line 46).

The instant invention is drawn to a dispersion which comprises an oily phase; an aqueous phase, in the form of an oil-in-water emulsion and at least one active

ingredient that is slightly or poorly soluble in the oily and aqueous phase, wherein the dispersion is free from toxicologically dangerous solvents.

Davis explicitly teaches a dispersion comprising an oil-in-water emulsion comprising a poorly soluble drug (Amphotericin B), which is administered parenterally, as similarly desired by the applicant. There is no significant distinction observed between the prior art and the instant invention since the prior art teaches the applicant's claimed desired objectives of a dispersion comprising an oil-in-water emulsion administered intravenously.

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Davis, who teaches an oil-in-water emulsion administered parenterally, comprising a poorly soluble drug (Amphotericin B) because Davis that the emulsions are stable and reduce the toxicity of the drug. The expected result would be an improved stable dispersion for the beneficial treatment of infectious conditions.

Regarding the instantly claimed amounts, Davis teaches similar amounts and percentages as desired by the applicant. Furthermore, it would have been obvious to one of ordinary skill in the art that suitable amounts and percentages could be determined through the use of routine or manipulative experimentation. Additionally and in the absence of showing any criticality, the applicant has not shown any unexpected results that accrue from the use of the instantly claimed amounts. The prior art teaches suitable concentrations to arrive at stable emulsions.

Kaufman teaches stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water (see abstract); (col. 1, line 64 through col. 2, line 60). The oil-in-water emulsion system includes a taxine, oil, water and a surfactant. More particularly, a taxine, such as taxol is solubilized in the oil in an effective pharmaceutical amount for intravenous administration. The taxine and oil mixture forms a dispersed phase in the water. Other taxines include taxotere, spicatin and others (col. 2, lines 3-8). Kaufman teaches that the oil may be any of a number of oils, such as mineral, vegetable, animal, essential and synthetic oils, hydrocarbons, paraffin oils or mixtures thereof. Preferably the oil is rich in triglycerides, such as safflower oil, soybean oil or mixtures thereof. Because taxol is more soluble in safflower oil than soybean oil, safflower oil is most preferred (col. 2, lines 10-15). The surfactant used may be a number of surfactants, and is usually a phospholipid, such as lecithin (col. 2, lines 15-17). The surfactant is needed to form stable emulsions.

Kaufman teaches that typically the taxine is present in an amount of about 0.1% to about 1% by weight of the emulsion. The oil is present in an amount of from about 1% to about 40% and the surfactant is present in an amount of about 0.5% to about 5% by weight of the emulsion. These ranges clearly read on the applicant's specified ranges.

The composition may also include further additives, such as glycerin, xylitol, mannitol, dextrose, Ringer's solution and sterols (col. 2, lines 23-36).

The examples demonstrate various preparations of emulsions comprising taxol. Example 1 shows results of a safflower oil solution containing 15 mg taxol/ml and 20 mg cholesterol/ml. This resulting composition is shown in Table 1. The particular ingredients used were lecithin, safflower oil, glycerin, cholesterol and taxol. Similarly, Example 2 shows the results for five different taxol formulations, wherein the mean particle sizes obtained were less than 1 nm, respectively (col. 4, line 47 through col. 6, line 46). In addition, the particle size was relatively constant over time, which further demonstrated the stability of the lipid emulsions of taxol.

The instant invention is drawn to dispersion which comprises an oily phase; an aqueous phase, in the form of an oil-in-water emulsion and at least one active ingredient that is slightly or poorly soluble in the oily and aqueous phase, wherein the dispersion is free from toxicologically dangerous solvents.

Kaufman teaches stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water (see abstract). There is no significant distinction observed between the prior art and the instant invention since the prior art teaches the applicant's claimed desired objectives of a dispersion comprising an oil-in-water emulsion administered intravenously.

Furthermore, the applicant has not demonstrated any unexpected results that accrue from the instantly claimed percentages or ranges. The prior art teaches similar amounts using the same composition.

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Kaufman, who teaches an oil-in-water emulsion administered for intravenous administration, comprising a poorly soluble drug (taxol) because, Kaufman teaches that such a composition would exhibit minimal side effects and successfully overcome the previous deficiencies of the prior art. The expected result would be a stabilized oil-in-water emulsion for administering taxol intravenously.

Prior Art made of record and deemed relevant by the examiner:

US Pat. No. 5,651,991 Sugiyama et al. (07/1997)

US Pat. No. 5,534,502 Seki et al. (07/1996)

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (703) 308-4429. The examiner can normally be reached on Monday through Friday from 7:00A.M. to 4:30P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

HNS
January 10, 2003

THURMAN K. PAGE
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